REMARKS

Claims 1-60 are pending, and subject to a restriction requirement. Claims 1-23 stand rejected and Claims 24-60 have been withdrawn from consideration. Claims 1, 13, and 20 are amended. Claims 2-12, 14-19 and 21-23 remain unchanged.

THE AMENDMENT

Claim 1 has been amended to recite the step of culturing the host microorganism in the presence of a suitable medium. Support therefor can be found, for example, at page 19, lines 15-17 of the Specification. Claim 1 has also been amended to describe the mevalonate pathway, as well as the steps involved in producing isopentenyl pyrophosphate. Support therefor can be found, for example, in Claim 10, and at page 5, lines 4-14 of the Specification.

Claim 13 has been amended to recite that *at least one* isopentenyl pyrophosphate is *reacted with dimethylallyl pyrophosphate or a polyprenyl pyrophosphate in the presence of at least one enzyme* to provide *a polyprenyl pyrophosphate isoprenoid precursor, which is then reacted with an enzyme* to form an isoprenoid.

Support for the *at least one* isopentenyl pyrophosphate language can be found, for example, in Claim 15, which recites various isoprenoids recited in Claim 15, where a monoterpenes requires a single isopentenyl pyrophosphate, a sesquiterpene requires two isopentenyl pyrophosphates, and so forth.

Support for the *reacted with dimethylallyl pyrophosphate or a polyprenyl pyrophosphate in the presence of at least one enzyme* and the *polyprenyl pyrophosphate precursor, which is then reacted in the presence of an enzyme* language and/or concept, can be found, for example, at page 26, lines 26-29, where it describes how the polyprenyl pyrophosphate precursor, farnesyl pyrophosphate, is produced from two molecules of isopentenyl pyrophosphate and one molecule of dimethylallyl pyrophosphate through the enzyme farnesyl pyrophosphate synthase, *ispA*. As is well known in the art, further enzymatic interaction with farnesyl pyrophosphate, produces the desired isoprenoid. See also, page 26, line 17 to page 27, line 13 of the Specification where it describes how geranylgeranyl pyrophosphate is produced from one molecule of farnesyl pyrophosphate and one molecule of isopentenyl pyrophosphate through the enzyme geranylgeranyl pyrophosphate synthase, *crtE*.

Claim 20 has been amended to correct a typographical error.

Neither the cancellation of claims nor the amendment of pending claims should be construed as abandonment of any originally claimed subject matter. Accordingly, the cancellation of claims or amendments herein is without prejudice to further prosecution in a continuation, continuation-in-part, divisional or other related application. No new matter has been added.

RESTRICTION REQUIREMENT

Claims 1-60 are subject to a restriction requirement. The Examiner has required restriction under 35 U.S.C. §121 to the following inventions:

I. Claims 1-23, drawn to a method for synthesizing isopentenyl pyrophosphate in a host microorganism comprising introducing into the host microorganism a plurality of heterologous nucleic acid sequences encoding for a different enzyme in the mevalonate pathway;

II. Claims 24-43, drawn to a method for synthesizing isopentenyl pyrophosphate in a host microorganism comprising introducing an intermediate in the mevalonate pathway and at least one heterologous nucleic acid sequence encoding an enzyme in the mevalonate pathway necessary for converting the intermediate into isopentenyl pyrophosphate; and

III. Claims 44-60, drawn to an isolated DNA fragment, expression vector and host cell.

Applicants elect, with traverse, invention I and Claims 1-23. This confirms the provisional election Applicants made in a telephone conversation with the Examiner on April 27, 2004. The non-elected Claims 24-60 are not canceled at this time, but they are retained of record in this application for later filing of divisional applications drawn to the subject matter thereon.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 13-21 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The Examiner submits that the phrase "isopentenyl pyrophosphate is further modified to provide an isoprenoid" renders the claim vague and indefinite. The Examiner then suggests

that reciting specific steps leading to the production of the isoprenoid may overcome the rejection.

Claim 13 has been amended to recite that at least one isopentenyl pyrophosphate is reacted in the presence of at least one enzyme to provide a polyprenyl pyrophosphate isoprenoid precursor (e.g., geranyl pyrophosphate, farnesyl pyrophosphate, geranylgeranyl pyrophosphate or higher order polyprenyl pyrophosphate), which is then reacted in the presence of an enzyme (e.g., a terpene synthase) to form an isoprenoid. Applicants assert that this language addresses the Examiner's rejection by indicating how the isopentenyl pyrophosphate is modified to provide an isoprenoid.

Accordingly, Applicants submit that Claim 13, as amended, and Claims 14-21 which depend therefrom, meet the requirements of 35 U.S.C. §112, second paragraph. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-23 stand rejected under 35 U.S.C. §112, second paragraph, as being incomplete fro omitting essential steps. The Examiner submits that the missing steps include culturing and isolation of the isopentenyl pyrophosphate. Claim 1 has been amended to recite an appropriate culturing step. However, no isolation step has been recited as the step is not necessary for the practice of the invention. For example, the isopentenyl pyrophosphate produced within the host organism, can be further modified while remaining within the host organism. See for example, page 20, lines 4-5 of the Specification, where it indicates that the isopentenyl pyrophosphate may be left in the host microorganism for further processing into the desired isoprenoid *in vivo*. Therefore, isolation is not required.

Accordingly, Applicants submit that Claim 1, as amended, and Claims 2-23 which depend therefrom, meet the requirements of 35 U.S.C. §112, second paragraph. Withdrawal of the rejection is therefore respectfully requested.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-4, 6-8, 10 and 12-23 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Claim 1, as amended, recites details to the mevalonate pathway, as well as the steps involved in producing isopentenyl pyrophosphate.

The Examiner has taken the position that the scope of Claim 1 is highly variant and includes many heterologous nucleic acids with widely differing structural, chemical, biological and physical characteristics which encode may heterologous enzymes. Applicants disagree. First, Claim 1, as amended, recites the role of each of the encoded enzymes by reciting each step in the pathway, e.g., facilitates the condensation of two molecules of acetyl-CoA to acetoacetyl-CoA, and so forth. Second, once the enzyme has been characterized, any structural, chemical, biological and physical diversity of the nucleic acid encoding such enzyme, becomes more clearly defined.

Therefore, Applicants submit that Claim 1, as amended, and the claims that depend therefrom, meet the written description requirement of 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

REJECTION UNDER 35 U.S.C. §102(b) OVER HOSHINO

Claim 1, 12, 13, 22, and 23 stand rejected under 35 U.S.C. §102(b) over EP 0955363 to Hoshino. Applicants note that Claims 2, 5-11, and 14-21 are not rejected under this section and appear to be free of the cited art.

Anticipation of a claimed invention by a prior art reference under 35 U.S.C. §102(b) requires the presence in a single prior art reference of each and every element of a claimed invention. *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F2d 744, 747 (CAFC 1986). Applicants respectfully submit that the cited reference to Hoshino fails to disclose each and every element of the presently claimed method.

In particular, Hoshino fails to disclose the specific steps recited in amended Claim 1, e.g., condensing two molecules of acetyl-CoA to acetoacetyl-CoA, and so forth. Instead, Hoshino discloses a pathway where the enzymatic conversion of mevalonate phosphate to mevalonate pyrophosphate is not even described (see, for example, Fig. 1 on page 57 of the Hoshino reference). Furthermore, the method described by Hoshino can not be conducted in *E. coli* and enzymatic activity in living cells was not established. These factors provide a disclosure that does not teach, or even suggest, the presently claimed method. As a result of these differences between the method described by Hoshino and that of the present claims, Hoshino cannot be said to anticipate the present invention.

As noted above, Claim 10 was not rejected under this reference. As the subject matter of Claim 10 is now recited in Claim 1, and in Claims 12, 13, 22, and 23, which depend therefrom, Applicants submit that amended Claim 1 is patentable over the Hoshino reference.

Accordingly, since the cited reference does not teach, or even suggest the invention as presently claimed, Applicants submit that the claimed invention is patentable under 35 U.S.C. §102(b).

REJECTION UNDER 35 U.S.C. §103(a) OVER HOSHINO IN VIEW OF TAKAGI

Claims 3 and 4 stand rejected under 35 U.S.C. §103(a) over Hoshino in view of Takagi et al. (2000), "A Gene Cluster for the Mevalonate Pathway from *Streptomyces* sp. Strain CL190," *Journal of Bacteriology* 182(15):4153-4157.

To establish a *prima facie* case of obviousness, the Examiner must present prior art references which, when combined or modified, teach or suggest all the claim limitations. However, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to teach or suggest all the claim limitations. In addition, there must be a reasonable likelihood of success, viewed in the light of the prior art. *Brown & Williamson Tobacco Corp. v. Phillip Morris Inc.* 229 F.3d 1120, 56 USPQ2d 1456, 1459 (CAFC 2000) citing *In re Dow Chem.*, 837 F2d 469, 473, 5 USPQ2d 1529, 1531 (CAFC 1988). Furthermore, the teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, and not in Applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (CAFC 1991). Based upon the foregoing requirements, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness.

The mevalonate pathways described by Hoshino and Takegi have significant differences, which would not lead one skilled in the art to attempt to combine their teachings, or to do so with any reasonable expectation of being able to successfully synthesize isopentenyl pyrophosphate in a host microorganism. For example, the pathway described in Fig. 1A of the Takegi reference (page 4154) includes malonyl-CoA, which is not present in the pathway described by Hoshino. Therefore, due the differences in the described pathways, there is no suggestion or motivation to

modify or combine the cited references. Further, there is no reasonable expectation that the teachings could be successfully combined.

As argued above, Hoshino fails to disclose the specific steps recited in amended Claim 1, e.g., condensing two molecules of acetyl-CoA to acetoacetyl-CoA, and so forth. This is similar to the subject matter of Claim 10, which was not rejected under the Hoshino teaching. This deficiency is not remedied by the Takagi teaching, as Takagi also does not teach or suggest the presently recited steps. Thus, even if the Hoshino and Takagi teachings were combined, they would not teach or suggest the presently claimed invention.

The Takagi reference describes the design of primers based upon genes taken from one section of the chromosome, which encompasses all the genes of the native form. Applicants' invention relates to the use of primers that were based upon the engineering and amplification of individual genes and resynthesis of biosynthetic operons. Finally, the Takagi reference begins its synthesis further downstream from the acetyl-CoA to acetoacetyl-CoA conversion recited in Claim 1. Therefore, irrespective of whether Takagi describes the use of a plurality of heterologous nucleic acid sequences contained in an extrachromosomal expression vector or in a single expression vector, as recited in Claims 3 and 4, there is nothing to suggest the method recited in Claim 1. And since Claims 3 and 4 must be read in light of the claim upon which they depend, the combined Hoshino and Takagi teachings fail to suggest the invention as claimed.

In conclusion, Applicants assert that a *prima facie* case of obviousness has not been established. Further, Applicants submit that Claim 1, as amended, is not anticipated by the Hoshino reference. Thus, as Hoshino fails as a primary reference, even if combined with the Takagi teachings, it would not render the claimed invention obvious. Accordingly, since the cited references, whether viewed alone or in combination, do not suggest the invention as presently claimed, Applicants submit that the claimed invention is patentable under 35 U.S.C. §103(a) and respectfully request withdrawal of the rejection.

SUMMARY

The above arguments and amendments to the Claims are submitted for the purpose of facilitating allowance of the Claims and a sincere effort has been made to place this application in condition for allowance. An early notice of allowance is earnestly requested. If in the opinion

of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 330-0900.

Respectfully submitted,

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